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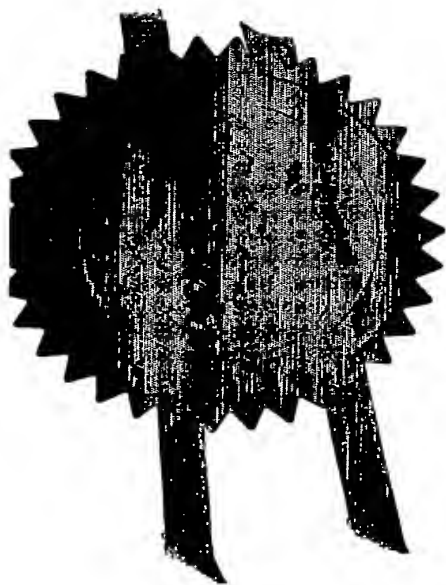
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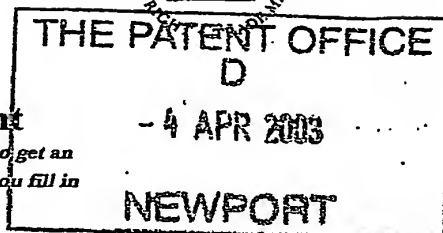
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2. Patent application number

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4 APR 2003

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Tissuemed Limited
11 Killingbeck Drive
Leeds
LS14 6UF

Patents ADP number (If you know it)

7826654001

If the applicant is a corporate body, give the country/state of its incorporation

England

4. Title of the invention

Tissue-adhesive formulations

5. Name of your agent (if you have one)

Adamson Jones

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

Broadway Business Centre
32a Stoney Street
Nottingham
NG1 1LL

Patents ADP number (if you know it)

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7975967001

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Number of earlier application

Date of filing
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Dr S A Jones

0115 9247 147

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Title — Tissue-adhesive formulations

Field of the Invention

- 5 This invention relates to materials suitable for use as tissue adhesives and sealants, and in particular to such materials that are formulated as loose or compacted powders.

Background of the Invention

10

There is considerable interest in the use, for a number surgical or other therapeutic applications, of materials that adhere to biological tissues eg as an alternative to the use of mechanical fasteners such as sutures, staples etc.

- Formulations of such materials that have hitherto been proposed include
15 viscous solutions or gels that are either manufactured in that form or are prepared immediately prior to use by mixing of the ingredients. Such formulations are then applied to the tissue surface using a suitable applicator device such as a syringe.

- 20 Formulations of the type described above suffer from a number of disadvantages. If the formulation is of low viscosity, it may spread from the area of application and hence be difficult to apply precisely to the desired area of tissue. If the formulation is more viscous, on the other hand, it may be difficult to dispense. In either case, the formulation, being prepared in
25 hydrated form, may have a limited lifetime and may be subject to premature curing. It may therefore be necessary for the whole of the formulation to be used at once or discarded. Also, the preparation of formulations immediately prior to use by mixing of ingredients is obviously laborious and time-consuming.

30

In addition to these drawbacks, the degree of adhesion between tissue surfaces that is provided by such formulations may be less than would be desired. As a result, it may be necessary to provide further reinforcement, eg

through mechanical attachment using sutures, staples or the like.

Alternatively, energy (eg light or heat energy) may be applied in order to initiate chemical bonding of the adhesive formulation to the underlying tissue, and hence bonding of the tissue surfaces to each other. Clearly, such

5 approaches introduce further drawbacks. The use of mechanical fastenings such as sutures or staples is often the very thing that the use of such products is intended to replace or avoid. In many instances the use of such fastenings is either not wholly effective (eg on the lung), or undesirable as their introduction gives rise to further areas of tissue weakness. The use of
10 external energy requires the provision and operation of a source of such energy. Such energy sources may be expensive and difficult to operate, particularly in the confines of an operating theatre or similar environment. Also, the use of external energy for attachment can be both time-consuming and (in some cases) requires significant careful judgement on the part of the
15 surgeon, to evaluate when sufficient energy has been delivered to effect attachment without damaging the underlying tissue.

There have now been devised improved formulations of tissue-adhesive materials that overcome or substantially mitigate the above-mentioned and/or
20 other disadvantages of the prior art.

Brief Summary of the Invention

25 According to a first aspect of the invention, there is provided a tissue-adhesive formulation comprising a naturally occurring or synthetic polymerisable and/or cross-linkable material in particulate form, the polymerisable and/or cross-linkable material being in admixture with particulate material comprising tissue-reactive functional groups.

30 The formulation according to the invention is advantageous primarily in that it can be easily applied to a tissue surface using a simple applicator or delivery device. As it is applied in solid form, the particulate formulation sticks to the moist tissue surface and does not spread unduly. On contact with the moist

tissue surface the formulation becomes hydrated, thereby causing reaction between the tissue-reactive functional groups and the underlying tissue surface. Reaction may also take place between the tissue-reactive functional groups and the other components of the formulation to form a strong, flexible and tissue-adherent gel. This formulation thus absorbs physiological fluids (as a consequence of application onto exuding tissue surfaces), combined with additional solutions used to hydrate the formulation following application (the fluids can be commonly used solutions used in surgical irrigation) becoming gelatinous and adherent to the tissue surfaces, and thereby providing an adhesive sealant, haemostatic and pneumostatic function.

In addition, the reaction between the tissue-reactive functional groups and the underlying tissue results in high adhesion between the formulation and the tissue surface, and hence between tissues that are joined using the adhesive formulation. Furthermore, because the formulation is made up in solid form that is, until hydrated by contact with the moist tissue surface (and subsequent hydration), essentially inactive, the formulation is not prone to premature reaction and as a result its shelf-life may be considerable. This further enables the formulation to be packaged in relatively large quantities that can be dispensed and used over a considerable time period, without the risk of substantial wastage.

The invention also provides a method of joining a tissue surface to another tissue, or of sealing a tissue surface, which method comprises applying to the tissue surface a formulation according to the first aspect of the invention.

Brief Description of the Drawings

Figure 1 is a schematic representation of the reaction between a tissue-reactive functional group (in the illustrated case an N-hydroxysuccinimide ester) and an amine-containing molecule such as a tissue protein.

Figure 2 shows the introduction of carboxyl group-bearing side chains into a poly(vinyl alcohol – vinyl acetate) copolymer.

5 Figure 3 represents the formation of a poly(N-vinyl-2-pyrrolidone-co-acrylic acid) copolymer.

Figure 4 shows the mechanism of free radical initiation of a polymerisation reaction.

10 Figure 5 illustrates the synthesis of a tissue reactive material.

Detailed Description of the Invention

Nature of the particulate material comprising tissue-reactive groups

15

The particulate material comprising tissue-reactive functional groups (hereinafter referred to as "tissue-reactive material") is preferably polymeric in nature. Most preferably, the polymer is a synthetic polymer.

20 By "tissue-reactive functional groups" is meant functional groups capable of reacting with other functional groups present in the tissue surface so as to form covalent bonds between the formulation and the tissue. Tissues generally consist partly of proteins, which commonly contain thiol and primary amine moieties. Many functional groups such as imido ester, p-nitrophenyl
25 carbonate, N-hydroxysuccinimide (NHS) ester, epoxide, isocyanate, acrylate, vinyl sulfone, orthopyridyl-disulfide, maleimide, aldehyde, iodoacetamide, and others, may react with thiols or primary amines, and therefore constitute "tissue-reactive functional groups".

30 Figure 1 illustrates the mechanism by which an NHS-functionalised polymer reacts with an amine-containing material such as a tissue protein represented by $R-NH_2$. The reaction is a nucleophilic displacement leading to the formation of an amide bond between the polymer and the tissue protein.

Tissue-reactive functional groups that may be of utility in the present invention are any functional groups capable of reaction (under the conditions prevalent when the formulation is applied to tissue, ie in an aqueous environment and

5 without the application of significant amounts of heat or other external energy) with functional groups present at the surface of the tissue. The latter class of functional group includes thiol and amine groups, and tissue-reactive functional groups therefore include groups reactive to thiol and/or amine groups. Examples are:

- 10 imido ester
- p-nitrophenyl carbonate
- N-hydroxysuccinimide (NHS) ester
- epoxide
- isocyanate
- 15 acrylate
- vinyl sulfone
- orthopyridyl-disulfide
- maleimide
- aldehyde
- 20 iodoacetamide

N-hydroxysuccinimide (NHS) ester is a particularly preferred tissue-reactive functional group.

- 25 In general, the tissue-reactive material may be formed by derivatisation of a suitable polymer precursor. Classes of polymer which lend themselves to such derivatisation include those that contain carboxylic acid or alcohol functional groups, or related structures. Polymers that may be used include polymers that are commercially available or polymers that are prepared
- 30 specifically for this purpose. Naturally-occurring materials such as sucrose or a derivatised cellulose may also be used.

Commercially available polymers that may be used include polyvinylalcohol (PVA). In the case of PVA, the functional groups may be introduced by first adding a chain extending or linking group, for example an acid functionality that can be further reacted with N-hydroxy succinimide. Figure 2 shows the addition of a chain-extending group to a copolymer of vinyl acetate and vinyl alcohol, the chain-extending group terminating in a carboxylic acid group that may be converted to the corresponding NHS-ester. The copolymer starting material (in which molar fraction x of vinyl alcohol groups may be 0.85-0.995) is reacted with a cyclic anhydride (in the example illustrated, succinic anhydride) in the presence of a base such as pyridine. Between 5% and 40% of the alcohol groups are derivatised to form the carboxylic acid-bearing side chains (ie $a+b=x$, with a being between $0.05x$ and $0.40x$), which may then be converted to the NHS-ester by conventional methods that are known *per se*.

Where the polymer support is synthesized for the purpose of subsequent derivatization, a wide variety of monomers may be used. Examples include N-vinyl-2-pyrrolidone, acrylic acid, vinyl acetate, vinyl acetic acid, mono-2-(methacryloyloxy)ethyl succinate, methacrylic acid, 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, (polyethylene glycol) methacrylate or other monomers containing acid or alcohol functionality. Such monomers may be polymerised via various standard polymerisation techniques, including free radical techniques using an initiator such as benzoyl peroxide, 2,2'-azobisisobutyronitrile (AIBN), lauroyl peroxide, peracetic acid etc. One preferred example of such a polymer is poly(N-vinyl-2-pyrrolidone-co-acrylic acid) co-polymer polymerised using AIBN. The polymerization of this material is illustrated in Figure 3, in which the molar ratio of acrylic acid-derived units may be between 0 and 1.0, preferably less than 0.60, and most preferably between 0.025 and 0.25. The copolymer may be further reacted with N-hydroxysuccinimide to form the tissue-reactive material.

Where, as is preferred, the tissue-reactive functional groups are NHS-esters, at least one of the monomers used in the preparation of the tissue-reactive

material must contain a carboxylic acid group or a group capable of being reacted with another material to form an acid functionality.

5 In the preferred case in which the tissue-reactive material is an NHS ester of poly(N-vinyl-2-pyrrolidone-co-acrylic acid) copolymer (PVP-co-PAA), the molar ratio of acrylic acid-derived units is preferably between 0.05 and 0.50, and hence that of the vinyl pyrrolidone-derived units is between 0.50 and 0.95.

10 The acrylic acid groups are preferably derivatised with NHS groups. A copolymer of PVP and PAA, in which the carboxyl groups of the acrylic acid-derived units carry NHS groups, is referred to herein as NHS-activated PVP-co-PAA.

15 As noted above, the activity of the tissue-reactive material (ie the degree to which the tissue-reactive functional groups of that material bind to the tissue) may be controlled by varying the proportion of that material in the formulation. The concentration of the tissue-reactive material in the formulation may be varied quite widely, eg from 10% w/w or less up to 50% w/w or more.

20

The formulation may contain one type of tissue-reactive material, or more than one type of tissue-reactive material.

25 Preferably, all or substantially all of the available sites in the precursor to the tissue-reactive material will be derivatised (ie the tissue-reactive functional groups will be introduced into all or substantially all of the available sites in the precursor to the tissue-reactive material). The degree of binding between the tissue-reactive functional groups and the tissue to which the formulation is applied will then be a function of the amount of tissue-reactive material in the
30 formulation.

Nature of the polymerisable and/or cross-linkable component

The polymerisable and/or cross-linkable component of the formulation is preferably selected from polysaccharides, polylactates, polyols and proteins, and derivatives thereof. The polymerisable component may be partially or fully cross-linked.

5

Proteins are preferred materials for the polymerisable and/or cross-linkable component of the formulation because they are rich in functional groups that are reactive to tissue-reactive functional groups. Hence, the tissue-reactive functional groups will react not only with the tissue surface to which the formulation is applied, but also with the polymerisable and/or cross-linkable component of the formulation.

10

A particularly preferred protein for use in the invention is albumin, particularly mammalian albumin such as porcine, bovine or human albumin.

15

Physical forms of the formulation

The formulation according to the invention may have the form of a loose powder, in which particles of the tissue-reactive material are admixed with particles of the polymerisable and/or cross-linkable component.

20

Alternatively, the formulation may take the form of a compacted body formed by compaction of the particles. Tissue-reactive materials based on poly (N-vinyl-2- pyrrolidone) or copolymers of N-vinyl-2-pyrrolidone with other monomers (eg vinylic monomers) are particularly preferred in such applications, as poly (N-vinyl pyrrolidone) has suitable flow properties for blending with other components of the formulation, and exhibits excellent performance in dry granulation tableting processes as it undergoes plastic deformation on compression, and has low hygroscopicity.

25

30

The formulation may further comprise additional components such as structural polymers, surfactants, plasticizers and excipients commonly used in tablet manufacture. Such further components may be present as discrete

particles, or may be components of the particles of tissue-reactive material and/or polymerisable and/or cross-linkable component.

Manufacture of the components and formulation

5

The particulate tissue-reactive material and the particulate polymerisable and/or cross-linkable component may be prepared by any suitable means. Particularly where the latter component is proteinaceous, the particles are preferably prepared by freeze- or heat-drying of an aqueous solution or
10 suspension. To enhance subsequent reaction of the proteinaceous material with the tissue-reactive material, the solution or suspension is preferably buffered to an alkaline pH prior to drying.

15

The formulation may be prepared simply by admixing the components in particulate form, and where desired compacting the formulation to form tablets, plugs or the like. The degree of compaction should be such that the tablets etc retain their integrity until applied to tissue, but not so great as to inhibit hydration (and hence adhesion) after application.

20

Therapeutic applications of the matrix

25

The formulation according to the invention is suitable for application to both internal and external surfaces of the body, ie it may be applied topically to the exterior of the body (eg to the skin) or to internal surfaces such as surfaces of internal organs exposed during surgical procedures.

The formulation is particularly suitable for surgical applications in the following areas:

30

Thoracic / cardiovascular

General surgery

ENT

Urology

- Oral / maxillofacial
- Orthopaedic
- Neurological
- Gastroenterology
- 5 Ophthalmology
- Gynaecology / obstetrics

Possible uses are described in more detail below.

10 *Wound healing*

The formulation may support and promote wound healing during both internal and topical procedures. Once the formulation begins to degrade, fibroblasts will move in and begin to deposit components of the extracellular matrix. The formulation therefore can be used as an internal or external dressing. In

- 15 addition, factors such as growth factors and cAMP that are known to promote the proliferation of skin cells may be added to the formulation to assist in the healing process.

Skin closure

- 20 The formulation may be applied topically to promote wound closure (as an alternative to sutures). This may have beneficial effects in that it may reduce scarring, and the formulation may thus be useful for cosmetic purposes during minor surgery (eg in Accident and Emergency Departments).

25 *Anastomosis*

The formulation provides a means of rapid sealing of, and prevention of leaks in, joined tubular structures such as blood vessels, and vascular and bladder grafts, and the GI tract.

30 *Sealing large areas of tissue*

The good sealing and handling properties of the formulation, combined with its self-adhesive properties and ability to cover a large surface area, mean that it

may be of particular use in sealing resected tissue surfaces – in particular those where diffuse bleeding is an issue (eg the liver).

Sealing air leaks

- 5 In addition to the patch properties described above, the high tensile strength and good inherent elasticity of the formulation (after hydration and reaction of the tissue-reactive functional groups), make it particularly suitable for sealing air leaks in the lung, particularly following lung resection.

10 *Haemostasis*

The formulation may be applied to a bleeding area, acting as a physical barrier. The tissue-reactive material in the formulation may immobilise proteins and thereby promote haemostasis.

15 *Therapeutic agent administration*

Drugs and other therapeutic agents (including biologically active agents such as growth factors, and even cells and cellular components) may be added to solution(s) used to form the components of the formulation, or covalently linked to components prior to their use in the manufacture of the formulation.

- 20 Once the formulation is in place, following application to the desired site, the drug will be slowly released, either by diffusion or by engineering the formulation so that as it degrades over time the drug is released. The rate of release can be controlled by appropriate design of the formulation. The formulation may thus provide a means of delivering a known amount of drug
- 25 either systemically or to a precise locus. The drug may be directly bound to a component of the formulation, or simply dispersed in the formulation.

The invention will now be described in greater detail, by way of illustration only, with reference to the following Examples.

30

Example 1

Synthesis of NHS-activated PVP-co-PAA

(a) Polymerisation of acrylic acid and N-vinyl-2-pyrrolidone

The polymer is formed via the polymerisation of monomers such as N-vinyl-2-pyrrolidone and acrylic acid, as shown in Figure 3.

5

A number of methods may be used to initiate the polymerisation, such as free radical, ionic (cationic or anionic), thermal, UV, redox etc. Free radical polymerisation is the preferred polymerisation method and 2-2'-azo-bis-isobutyronitrile (AIBN) is the preferred initiator. The AIBN decomposes into

10 two radicals which can then attack the carbon-carbon double bond in the vinylic monomer (acrylic acid) as shown in Figure 4.

This will continue until termination of chain growth, via combination, disproportionation etc.

15

The reaction solvent may be N,N'-dimethylformamide, toluene, or any other suitable solvent with a boiling point greater than 100°C. Toluene is the currently preferred solvent.

20 A typical polymerisation method is as follows:

Solvent is charged to the reaction flask, usually around 5-10ml of solvent per gram of monomer used is sufficient. The solvent is heated in an oil bath to a temperature sufficient for the generation of free radicals from the chosen

25 initiator, 80-85°C is the optimum temperature when using AIBN as the initiator. Oxygen-free nitrogen is bubbled through the solvent to remove any dissolved oxygen. Oxygen is also removed from the monomers in the same manner. The initiator is added to the solvent and allowed to dissolve. The monomers are added and the vessel closed. A nitrogen inlet and an escape

30 needle may also be used.

The reaction is allowed to stand for around 3-6 hours, with 6 hours being the preferred reaction time. The reaction mixture is cooled and the polymer is

isolated from the solvent/polymer solution by precipitation in 5:1 hexane/isopropanol followed by filtration. Successive washes with diethyl ether are required to remove all traces of polymerisation solvent from the polymer. After 4-5 diethyl ether washes the polymer is dried under reduced pressure to constant weight.

Typical reaction conditions are shown in Table I:

Table 1

Solvent (vol)	Monomer (g)		AIBN (g)	T (°C)	Time (hrs)	Yield	Mn	Mw	Polydispersity Index
	acrylic acid	N-vinyl-2- pyrrolidone							
Toluene (100ml)	8.5 (80mol%)	1.5 (20mol%)	0.02 (0.125%)	80	3	-	-	-	-
Toluene (100ml)	9.3 (90mol%)	0.7 (10mol%)	0.02 (0.125%)	80	3	54%	80040	38800	2.0
Toluene (100ml)	9.3 (90mol%)	0.7 (10mol%)	0.04 (0.25%)	80	3	58%	74240	38340	1.9
DMF (100ml)	9.3 (90mol%)	0.7 (10mol%)	0.02 (0.125%)	80	3	62%	54000	25150	2.1
Toluene (100ml)	9.5 (92.5mol%)	0.5 (7.5mol%)	0.02 (0.125%)	80	3	-	-	-	-
Toluene (100ml)	9.65 (95mol%)	0.35 (5mol%)	0.2 (0.125%)	80	3	-	-	-	-

(b) Reaction of PVP-co-PAA and N-hydroxysuccinimide in the presence of dicyclohexylcarbodiimide

NHS-activated PVP-co-PAA is formed from the reaction of PVP-co-PAA and N-hydroxysuccinimide in the presence of dicyclohexylcarbodiimide (Figure 5).

10g of PVP-co-PAA containing 0.094 moles of acrylic acid repeat units is dissolved in 50 ml of dried N,N'-dimethylformamide by stirring in a dry 100ml round bottomed flask. 0.01 moles of N-hydroxysuccinimide (1.15g) is added to the polymer solution and is allowed to dissolve.

Dicyclohexylcarbodiimide (2.06g) is melted in an oven at 60°C and added to the polymer solution. This is left to stir at room temperature for at least 24 hours. The formation of a white precipitate (dicyclohexylurea) is observed. After 24 hours the precipitate is removed by filtration, and the flask and filter washed with a small amount of dry DMF. The polymer is isolated by precipitation in 5:1 hexane/isopropanol and filtration. The polymer is further purified by repeated washes with dry diethyl ether. The yield is between 50-70%.

Example 2

Blending of NHS-activated PVP-co-PAA with freeze-dried porcine albumin and application to liver tissue

Powders of NHS-activated PVP₈₀-co-PAA₂₀ copolymers have been blended (1:1) with freeze dried porcine albumin (previously buffered to pH 10.5) and delivered onto moist liver tissue. The powder rehydrated rapidly (< 5 minutes) yielding a gel that offers cohesive strength, in addition to offering strong adhesion to the underlying tissue surface.

Example 3

Blending of NHS-activated PVP-co-PAA with freeze-dried human albumin and application to liver tissue

Powders of NHS-activated PVP₇₀-co-PAA₃₀ copolymers have been blended (1:1) with freeze-dried human albumin (Baxter human albumin infusion (20%) previously buffered 1:1 with to pH 10.5 buffer) and delivered onto moist liver tissue. The powder rehydrated rapidly (< 5 minutes) yielding a gel that offers cohesive strength, in addition to offering strong adhesion to the underlying tissue surface.

Example 4

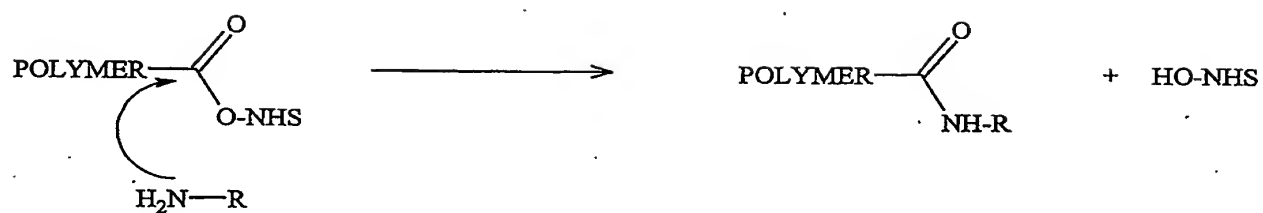
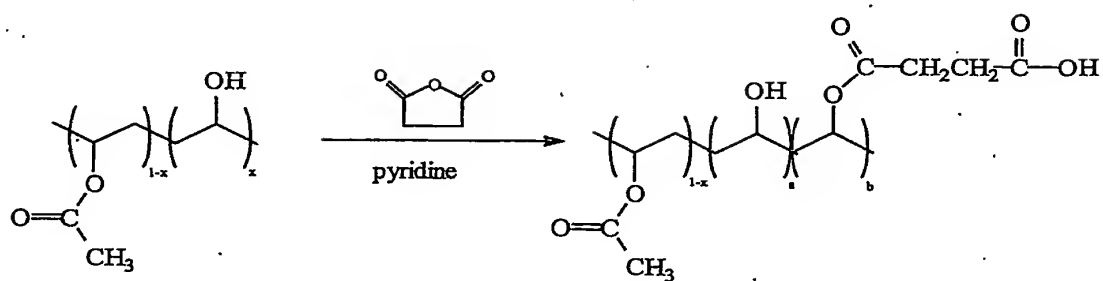
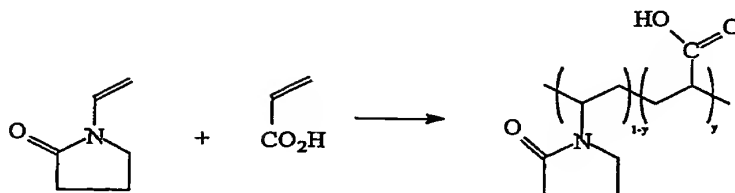
Blending of NHS-activated PVP-co-PAA with freeze-dried porcine albumin, forming a compressed disc followed by application to liver tissue

Powders of NHS-activated PVP₇₀-co-PAA₃₀ copolymers have been blended (2:1) with freeze dried porcine albumin (previously buffered to pH 10.5 buffer), followed by compression into a thin (<2mm thick) disc and delivered onto moist liver tissue. The disc adheres immediately to the liver tissue and rehydrates gradually over an hour yielding a gel that offers cohesive strength, in addition to offering strong adhesion to the underlying tissue surface.

Example 5

Blending of excipients with powdered PVP(NHS)₂₀ and freeze-dried porcine albumin previously buffered to pH 10.5 (PSA)

Powders of PVP(NHS)₂₀ and PSA (1:1) have been blended with excipients such as hydroxypropyl cellulose, poly(vinyl pyrrolidone) and microcrystalline cellulose. The powdered mixture was compressed into a disc with a thickness of less than 2mm. These discs adhered immediately to moist porcine liver tissue and rehydrated upon immersion in aqueous solution. After immersion in aqueous solution for 1 hour, they remained adhered to tissue as a crosslinked gel. Adhesion was obtained with concentrations of PVP(NHS) and PSA from 11.5% to 50% w/w.

Figure 1Figure 2Figure 3

CC(C)(C#N)=[N+]#N[CH-](C#N)C \longrightarrow $2 \text{ } \text{CC(C)(C#N)[CH-]}$ + $\text{N}\equiv\text{N}$
CC(C)(C#N)[CH-] + C=C(C(=O)O) $\xrightarrow{\text{CO}_2\text{H}}$ CC(C)(C#N)C(C(=O)O)C(C(=O)O)[CH-] \longrightarrow \longrightarrow \longrightarrow

Chemical reaction scheme showing the conversion of a poly(amide-imine) with a carboxylic acid side group to a poly(amide-imine) with a succinimide side group. The reaction uses DCC and N-methylsuccinimide as reagents.